REMARKS/ARGUMENTS

1. Claims 10, 19-36, 41 and 42 have been previously withdrawn from consideration as being drawn to a non-elected invention and species. Claims 37, 39 and 40 have been previously canceled and claims 43 and 44 have been previously presented. Claims 1, 3, 4, 17, 18, 43 and 44 are currently amended. Claim 45 is newly presented.

Part (d) of claims 1, 3, 4, 17, 18 and 44 have been amended to include additional agents found on page 20, lines 17-28 of the specification.

Claim 43 has been amended to reference SEQ ID NO:9. for L104EA29YIg. Support for this amendment may be found on page 9, lines 23-29; page 12, lines 2-7; and in Figure 6 of the specification.

Support for new claim 45 may be found on page 9, lines 8-29 and page 12, lines 2-7.

Rejection under 35 U.S.C. § 112, first paragraph

2/3. Claim 43 and 44 have been rejected under 35 U.S.C. § 112, first paragraph for failing to comply with the enablement requirement. The claims recite a nucleic acid sequence included in ATCC Deposit No: PTA-2104 which is required to practice the claimed invention.

The DNA required to practice the claimed invention is readily available to the public by a deposit made under the terms of the Budapest Treaty. Applicant's representative hereby gives the following assurance by signature below:

Bristol-Myers Squibb Company, an assignee of the present application, has deposited biological material under the terms of the Budapest Treaty on the International Recognition of the Deposit of Micro-organisms for the Purposes of Patent Procedure with the following International Depository Authority: American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, Virginia 20110-2209. The deposit comprise the DNA sequence, L104EA29YIg, of the present invention. The deposit was made on June 19, 2000, and given ATCC Accession Number PTA-2104. In accordance with MPEP 2410.01 and 37 C.F.R. § 1.808, assurance is hereby given that all restrictions on the availability to the public of ATCC Accession Number PTA-2104 for the

L104EA29YIg sequence will be irrevocably removed upon the grant of a patent based on the captioned application, except as permitted under 37 C.F.R. § 1.808(b).

Applicant's representative also hereby gives the following additional assurance by signature below:

In accordance with 37 C.F.R. § 1.805 to § 1.807, assurance is hereby given that the viability of the deposit for L104EA29YIg sequence, made on June 19, 2000, and given ATCC Accession Number PTA-2104, will be maintained during the pendency of the captioned application for a duration of at least 30 years or at least five years after the most recent request for the furnishing of a sample of the deposit is received by the ATCC, or whichever is longer; and that the deposit will be replaced if it should ever become inviable.

Rejection under 35 U.S.C. § 112, second paragraph

4. Applicants acknowledge that the previous rejections under 35 U.S.C. § 112, second paragraph, with respect to the recitations of "regulating":, "etanercept", and "anakinra" have been obviated by previous amendments.

5. Claims 1-9, 11-18 and 38 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) The Examiner has found claims 1-9, 11-18 and 38 to be indefinite in the recitation of "consisting of administering" and "(d) optionally, at least one pharmaceutical agent selected from the group … nonsteroidal anti-inflammatory drugs, any biological agent targeting an inflammatory cytokine…" because the claims appear to be open and closed at he same time with respect to type and nature of agents that are administered for inhibiting cell-mediated immune responses or treating an immune system disease.

Part (d) of independent claims 1, 3, 4, 17 and 18 has been amended to include a specific group of agents thereby limiting the options to those agents listed. The Applicants believe that the claims read to a method requiring a first agent, a second agent and a third agent that may be

administered with or without agents listed in part (d). Therefore the claim is closed as the agents being administered are limited to those listed.

B) The Examiner has found claims 43-44 to be indefinite in the recitation of "L104EA29YIg" because its characteristics are not known and not clearly defined.

While the Applicants believe that the reference to the sequence described in Figure 6 clearly defines the L104EA29YIg molecule, in order to advance prosecution, the Applicants have amended claim 43 to reference SEQ ID NO:9. for L104EA29YIg as suggested by the Examiner. The position numbers have changed as the numbering system in SEQ ID NO:9 includes the leader sequence attached to the N-terminus of the molecule.

C) Support for this amendment may be found on page 9, lines 23-29; page 12, lines 2-7; and in Figure 6 of the specification. No new matter has been added.

7. The Applicants acknowledge the obligation under 37 CFR 1.56 and confirms that the Examiner may presume that the subject matter of the various claims was commonly owned at the time the inventions covered herein were made.

Rejection under 35 U.S.C. § 102

6/8. Claims 1-7, 9, 12-18 and 38 have been rejected under 35 U.S.C. 102(e) as being anticipated by Digan et al. (US2002/0142000).

The Applicants have addressed the Examiner's concern that the claims are open to the immunotoxins described in Digan by deleting the phrases "nonsteroidal antiinflammatory drugs" and "any biological agent targeting an inflammatory cytokine" thereby, narrowing the agents recited in part (d) of claims 1, 2, 4, 17 and 18 to a specific listing of agents that do not include the immunotoxins of Digan.

While Digan teaches that anti-CD3 immunotoxins may be used in combination with other agents effective in treating acute or chronic transplant rejection (paragraph 0198), Digan specifically teaches that a "combined administration is meant treatment of the organ transplant recipient with

both an anti-CD3 immunotoxin of the invention and the spergualin derivative or analog" (paragraph 0209). Digan does not teach the combination of any three of the listed "other agents" found in paragraph 0198 with or without the anti-CD3 immunotoxins or teach any benefits of combinations.

The Applicants believe that the amended claim language results in a real difference in the claimed method steps when compared to the prior art, specifically anti-CD3 immunotoxins are not included in the claimed invention.

Rejection under 35 U.S.C. § 103(a)

9. Claims 1-9, 12-18 and 38 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Blazer et al. (WO95/34320) in view of Larsen et al. (US patent 5,916,560), Strom et al. (Therapeutic Immunology, Austen et al. (Ed.) Blackwell Science, Cambridge MA, 1996, pages 451-456), Kenyon et al. (US 2003/0072754) and Kirk et al. (US 2002/0119150) Applicants respectfully disagree.

As pointed out above, the Applicants have addressed the Examiner's concern that the method claims appear to be open and closed with respect to the type and nature of agents that are administered by limiting the optional group to a specific listing of agents.

The Applicants are not able to respond to the comments regarding the Dana et al. reference (found on page 6 of the Office Action) as the specific reference data has apparently been inadvertently left out of the above referenced Office Action. However, the Applicants will address the newly cited Kenyon et al. and Kirk et al. references.

Kenyon et al. teaches the use of a CD40:CD154 binding interrupter used alone or in combination with another therapeutic agent , such as an immunomodulatory agent or a tolerizing agent to attenuate, suppress, prevent, delay or reverse counter-adaptive immune system rejection of grafted insulin-producing tissue in a recipient host, without the need for pan-suppression of the recipient's immune system (paragraph 0007). As cited by the Examiner, paragraph [0051] teaches that combination therapies include the use of anti-CD40L antibodies together with agents that may be targeted at B cells or alternatively agents targeted at T cell/ B cells. Kenyon does not teach or provide motivation to combine more than one agent from paragraph [0051].

Similarly, Kirk et al. teaches the use of a CD40:CD154 binding interrupter in combination with another immunosuppressant or immunomodulator, specifically with an agent that blocks

costimulation via CD28(paragraph 0005). Paragraph [0057] teaches that combination therapies include the use of anti-CD40L antibodies together with agents that are targeted at B cells or alternatively agents targeted at T cell/ B cells. Kirk does not teach or provide motivation to combine more than one agent from paragraph [0057].

The teachings of newly cited Kenyon and Kirk do not provide the missing motivation to combine more than two agents. In fact, both Kirk et al. and Kenyon et al. reinforce the double therapy pathway described in Blazer and Larsen. If Blazer is considered in view of Larsen, Kirk and Kenyon and the basic principles set forth in Strom et al., at best, the skilled person would consider the use of the standard of therapy agents described by Strom in Table 36.1 in combination with the double therapy pathway described in Blazer, Kirk, Kenyon or Larsen. There would be no motivation to combine an agent that blocks the CD28/CTLA4/B7 pathway with and an agent that blocks the gp39/DC40 pathway and an agent that inhibits adhesion of the T cell, with or without the standard of therapy immunosuppressants of Strom especially since Blazer teaches the use of either anti-LFA-1 antibody or anti-gp39 antibody.

Further, the common goal of each of these references is to provide treatments that are effective with less toxicity than currently available therapeutic agents. One would not intuitively accomplish this goal by adding multiple standard of therapy agents, each with their own inherent risks of toxicity, to a treatment protocol. Typically, the more agents administered to a patient, the more complicated the treatment plan becomes. The physician is motivated to decrease the number of therapeutic agents administered to a patient, not increase the number.

In view of the lack of evidence showing the claimed invention is obvious in view of the cited references, Applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 1-9, 12-18 and 38, under 35 USC 103(a).

10. Claims 6, 8 and 11 are rejected under 35 USC 103(a) as being unpatentable over Blazer et al. (WO95/34320) in view of Larsen et al. (US patent 5,916,560), Strom et al. (Therapeutic Immunology, Austen et al. (Ed.) Blackwell Science, Cambridge MA, 1996, pages 451-456), Kenyon et al. (US 2003/0072754) and Kirk et al. (US 2002/0119150), as applied to claims 1-9, 12-18 and 38 above and further in view of the known availability of the deposited material producing the known immunosuppresives selected from the group consisting of CTLA4, anti-CD40 antibiotics and anti-LFA-1 antibodies as acknowledged on pages 15-16 of the instant specification and cited in published references. Applicants respectfully disagree.

Since Blazer et al., in view of Larsen et al., Kenyon et al., Kirk et al., and Strom et al. do not render obvious the claimed methods for the reasons discussed above, the fact that reagents of the claimed methods were publicly available does not provide the motivation to one skilled in the art to combine the three claimed agents with or without the standard of practice agents described by Strom. Accordingly, the Applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 6, 8 and 11, under 35 USC 103(a).

11. Claims 1-9, 11-18 and 38 are rejected under 35 USC 103(a) as being unpatentable over Digan et al.(US 2002/014200 A1) in view of Strom et al. (Therapeutic Immunology, Austen et al. (Ed.) Blackwell Science, Cambridge MA, 1996, pages 451-456) and known availability of the deposited material producing the known immunosuppresives selected from the group consisting of CTLA4, anti-CD40 antibiotics and anti-LFA-1 antibodies as acknowledged on pages 15-16 of the instant specification and cited in published references. Applicants respectfully disagree.

As pointed out above, the Applicants have addressed the Examiner's concern that the method claims appear to be open and closed with respect to the type and nature of agents that are administered by limiting the optional group to a specific listing of agents.

At best, being aware of the basic principle of multiple therapy described in Strom along with the standard of practice agents listed in Strom and the immunotoxin described in Digan, one skilled in the art would be motivated to add the immunotoxin to a standard multiple therapy described in Strom. The fact that the reagents of the claimed methods were publicly available does not provide the motivation to one skilled in the art to combine the three claimed agents with or without a standard of practice multiple therapy minus the immunotoxin described in Digan.

Applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 1-9, 11-18 and 38, under 35 USC 103(a).

12. Claims 6, 8 and 11 are rejected under 35 USC 103(a) as being unpatentable over Blazer et al. (WO95/34320) in view of Larsen et al. (US patent 5,916,560), Strom et al. (Therapeutic Immunology, Austen et al. (Ed.) Blackwell Science, Cambridge MA, 1996, pages 451-456), Kenyon et al. (US 2003/0072754) and Kirk et al. (US 2002/0119150), as applied to claims 1-9, 12-18 and 38 above and further in view of Peach et al. (US2003/0219863). Applicants respectfully disagree.

While one of ordinary skill in the art might have been motivated by Peach et al. to substitute L104EA29YIg for CTLA4Ig in the combination therapies taught by Blazer et al., they would be motivated to administer a double therapy at most because the L104EA29YIg binds with higher avidity than CTLA4 thereby being more effective and consequently requiring fewer agents to treat the immune system disease.

Applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 6, 8 and 11, under 35 USC 103(a).

Respectfully submitted,

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